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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 01/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/585,475	ANDERSON ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-94,96 and 97* is/are pending in the application.

4a) Of the above claim(s) *14-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *85-94 and 96-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The Amendment under 37 CFR § 1.111 filed on Sep. 10, 2003 is acknowledged. Claims 1-13 and 95 are cancelled; claims 14-94 and 96 to 97 are pending in the application. Claims 85-94 and 96-97 are the subject of this Office Action; claims 14-84 are withdrawn from consideration as drawn to the non-elected invention.

Office Action

1. Objections

Claim 93 is objected to because it contains the typographical error "claim10" introduced by amendment. Claim 94 is objected to because it contains typographical error "antipipemic".

Objection to claim 85 is withdrawn.

2. Rejections

2.1 35 USC, section 112, second paragraph

Claim 85-94 and 96-97 are still rejected for the use of term "a degree of effective' response and "a degree of efficacy", or "a degree of effective response", of an agent, because neither the claims nor the specification define the term efficacy. As indicated in the previous Office Actions it is unknown to what word efficacy is related. Is this an efficacy of a drug in the treatment of a particular disorder? How the degree of efficacy is defined? The indefinite term and phrase render the claims indefinite.

In their response Applicants write, "the terms "efficacy" as well as "toxicity" (which is apparently clear to the examiner) are both relative terms and frequently dose

dependent." Further Applicants state, "Thus, the term 'degree of efficacy' as used in the claims is determined by the result from comparison".

This argument has been fully considered but is found not persuasive for the following reasons. It is clear to the person skilled in the art that the term efficacy is a relative term and efficacy is dose dependent. This is, however, not a point. The term efficacy is unclear absent a statement of what effect is referred to. While some "effects" might be obvious on their face from an agent, many compound included within the scope of "agent" would not have any associated effect or may have multiple different effects. The general, not questionable meaning of the term has too broad scope, and one skilled in the art would not know what is included or excluded from the scope of the claim. Thus, as stated in the previous Office Action, paper No. 10, in order to examine claim 85, it is assumed that the efficacy of an agent is any change it causes in the kind and content (concentration in the tissue) of the proteins isolated from the exposed tissue as compared to unexposed tissue or the same tissue exposed to an agent for which said changes are already known. In addition, claim 88 recites the phrase "relative amount of toxicity or effectivness", which is not defined in the claim or the specification.

Claims 96 recites the terms "effective amount" and "greater then effective amount", which are not defined by the claim or specification. The claims and specification do not define what the amount must be effective for.

In response to this rejection Applicants inform they amended the claim to contain the word "dosage" instead of "amount", however, the filed claim 96 is not amended.

The examiner acknowledges amendment to claim 85; the amended claim 85 is properly depedent.

2.2. *35 USC section 112, first paragraph*

Rejection of claim 85-94 and new claims 96-97 are rejected under 35 U.S.C. 112, first paragraph for reasons made the previous Office Action, paper No.10 and reiterated herein.

The specification fails to describe a degree of toxicity and/or efficacy and its measurements. The disclosure is enabling for determining changes in the presence and/or level of markers in a proteome, wherein the changes are caused by exposure of a tissue to tested chemicals. On page 6, line 26 the Applicants write: "Sets of perturbed protein markers provide a proteomic pattern or 'signature' indicating relative toxicity and/or efficacy." **It is not toxicity or efficacy that is measured. It is the ratio of levels of the marker protein after exposure to a new chemical and a standard or untreated control that may be quantified.**

Examples presented by Applicant are silent about how to perform measurements of toxicity and efficacy. Thus, the disclosure is not enabling for a quantitative assay of toxicity/efficacy. The disclosure is enabling for visualizing the changes in the proteome induced by any agent and measuring the levels of the marker proteins. These measurements may be used further for calculating the ratio of the levels of the marker proteins after treatment with a tested drug and a standard drug or untreated control.

In response to this arguments Applicants assert, "the amount of certain specific proteins (one or more of those claimed) does correlate to the 'efficacy' of the agent when compared to a positive an/or negative control."

The argument is not persuasive, because one skilled in the art is aware that for some drugs and marker proteins the dependence of the level of the marker upon the level of biochemical changes in organism exposed to the drug are well established. However, Applicants, themselves do not teach any calibration curve that would represent **a relationship between toxic effects measured by, for example,** increased blood transaminases (see page 15, line 9) **and changes in the level of particular marker/markers in the proteome**. The disclosure also fails to teach any calibration curve for **efficacy of a drug, as for example** a relationship between the level of cholesterol in the blood after treatment with a particular drug and **a level of particular marker/markers in the proteome.**

The claimed subject matter is broad and includes unpredictable changes in the levels of proteins in the cell in response to the exposure to a drug or toxic agent. The quantity of some proteins may change in linear fashion; the amount of some proteins may be unaffected; some may disappear completely; some may change only after exposure to a certain threshold level of agent or may change in non-linear fashion. As such it would require undue experimentation to use any one or more protein markers to determine the efficiency or toxicity of a candidate agent absent guidance regarding how

each marker changes in response to such agents and how the change correlate to toxicity and /or efficacy.

A skilled artisan concludes, therefore, the claimed subject matter was not described in the specification in such full, clear, concise and exact terms as to enable any person skilled in the art, to which it pertains, to use the invention.

In their response Applicants argue, "A quantitative measurement relative to a standard is a quantitative measurement".

The examiner agrees the comparison of concentration of a marker in its spot after treatment with a tested compound and a standard is quantitative. However, one skill in the arts still does not know what biologic effect is involved, because the claims do not define it. So the question, "Efficacy of what is reflected by such and such increase (decrease) in the concentration of a marker relative to the standard?" is not answered.

Applicants' position is, "The examiner elaborates by urging that a calibration curve is not taught. This is not correct. For example, in Table 2 of the specification, many examples [of calibration curves?] are readily seen by simple scanning. Bellow are some examples form the first three proteins and the last three proteins from Table 2:" and further, "While the proportional change with changing pharmaceutical dosage does differ from

protein to protein, one can still see that a calibration curve can be drawn."

This argument is found not persuasive. It is against the rules in the art to treat a straight line joining two points as a calibration curve, because two experimental points cannot be predictive about the real shape of the curve. As indicated above, the quantity of some proteins in their spots may change in linear fashion, but many, if not most, of chemical agents have a non-linear calibration curve.

The Applicants furthermore contend the examiner criticizes specification, because "protein changes are not correlated to level of cholesterol in the blood of humans being treated with the drug."

Examiner has not criticized the specification for the mentioned reason. That what examiner wrote in the previous Office Action and reiterated above is; "Applicants do not teach any calibration curve that would represent a relationship between toxic effects measured by, for example [emphasis added], increased blood transaminases (see page 15, line 9) and changes in the level of particular marker/markers in the proteome. The disclosure also fails to teach any calibration curve for efficacy of a drug, as for example [emphasis added] a relationship between the level of cholesterol in the blood after treatment with a particular drug and a level of particular marker/markers in the proteome. In addition, the claimed subject matter is broad and includes unpredictable changes in the levels of proteins in the cell in response to the exposure to a drug or toxic agent."

The examiner has noted that the specification uses high and low dose of the tested drugs. The claims however, do not recite the measurement of toxicity and efficacy as determined at low and high doses of a drug. The claims are directed to the method that comprises "exposing a tissue of interest in a subject ". One skilled in the art understands the meaning of the phrase "exposing a tissue of interest in a subject " as the exposure to a single dose. In addition, claims 90, 93, 96 and 97 recite "pharmaceutically appropriate amount", "effective amount" and "toxic amount", respectively. Thus, there is no doubt that the claims are directed to single dose of an agent.

In conclusion, the current language of the claims refers to comparison of proteome of the tissue exposed to a dose of the tested drug with that of a dose of drug for which the characteristics of proteome is already known, or with proteome for unexposed control, thus enabling quantifying the ratio of concentration of marker proteins after both exposures.

2.3. 35 USC section 103

Claims 85-94 and new claims 96-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson at al. (A two-dimensional gel database of rat liver proteins useful in gene regulation and drug effects studies, *Electrophoresis*, **1991**, 12, 907-903) and Anderson et al. (An updated two-dimensional gel database of rat liver proteins useful in gene regulation and drug effect studies *Electrophoresis*, **1995**, 16, 1977-1981) and further in view of Anderson et al. (The effects of perioxisome

proliferators on protein abundance in mouse liver, Toxicology and Applied Pharmacology, **1996**,137, 75-89).

The claimed invention comprises testing an agent using display of proteome by two dimensional electrophoresis and measurements of levels of 175 protein markers listed in claim 85 and 112 markers listed in claim 86, wherein alternatively two control samples might be used. One of the controls is from the same tissue not treated with any agent, the other from the same tissue exposed to an agent of known toxicity or efficacy.

Anderson and her co-workers (1991) exposed liver tissue in rats to antilipemic agents lovostatin, or lovostatin in combination with cholestyramine, or to none of the chemicals. The animals were sacrificed and livers removed, proteins extracted, and the levels of protein markers were measured in the liver proteome using two-dimensional electrophoresis. All protein markers listed in claim 85 and 86 of the instant application, total of 234, and at least three markers identified by full names in claim 85 of the instant application (actin gamma, apo A-I lipoprotein, HMG-CoA, and catalase) are already listed in Table 1 and 2 of Anderson 91 paper; see copies of the tables with marked positions. In addition, in her paper from 1995 Anderson provides further identification of the marker known previously as MSN. The markers listed in Anderson 95, in Table 1 on page 1978, are called "useful in drug effect studies". Table I of Anderson 1995 contains many markers listed in full names in claim 85 of the instant application; see the copy of Table 1 of Anderson 95 with examiners' markings of the respective markers.

Anderson at al. 1991, do not teach using alternatively two control samples; they use as control only unexposed sample. However, Anderson et al 1996 teach effects of

peroxisome proliferators on mouse liver proteome. Among others, they study the drug called LY171883, at a range of doses, and they use another peroxisome proliferator LY163443 as a negative control. The quantitative changes in amount of cytosolic epoxide hydrolase, 80 kDa bifunctional enzyme, and unidentified spot IEF163 induced by different doses of LY171883 are presented in Fig. 8, page 86; copy enclosed.

It would have been obvious to one having ordinary skill in the art at the time of invention to have the method described by Anderson 1991, and if necessary, apply as a control the proteome from unexposed tissue, but also, as Anderson 1996 did, from the same tissue treated with an agent considered to be a standard in particular screening. In the art, it is routine to compare effects of two drugs, and it has been done in all methods known before the Applicants filed the application. Therefore, including, in alternative, the second control is not novel or inventive.

It would also have been obvious to one having ordinary skill in the art at the time of invention to have the method described in Anderson et al 1991, and modify it by using as markers of efficacy the markers of claims 85 and 86 of the instant Application because the very markers are listed by Anderson et al. as "protein useful in drug effect studies"; see the enclosed, marked, copy of Table 1 of Anderson et al. 1995.

The motivation would be to apply the proteome visualization in a method of screening for toxic and pharmacologic effects of potentially new drugs. This motivation is provided by Anderson at al. 1991, because their data, see Figure 10 and its description, clearly suggest that the proteome markers can be used to "show

quantitative effects of various treatments" on mammalian tissue. The motivation is also provided by Anderson et al. 1996 by the title of the article.

The expectation of success is very high, because exposure of a tissue to a chemical always result in some changes in protein expression, synthesis and metabolism, and these changes are manifested by changes in the presence and/or level, of toxicity and/or efficacy markers in the proteome. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Traversing this rejection Applicants argue is that such markers as gamma actin, apo A-I lipoprotein and catalase taught as protein markers in proteome of rat liver were found not to change in aboundance with drug treatment and for that reason although Anderson teaches these markers, her article teaches away from the present invention.

This argument has been fully considered but is found not persuasive.

Firstly, when a protein in proteome has its biological function assigned one skilled in the art can predict whether the level of protein in the spot will change after exposure to certain drug; assuming that it is known in which metabolic pathway the drug is involved. Thus, there is nothing supprising that antilipemic drug tested by Anderson (1991) did not change expression and/or synthesis of actin gamma which is a cyoskeletal protein not involved in cholesterol synthesis. The negative result with actin gamma and cholesterol metabolism targeting drugs does not exclude use of actin gamma for monitoring activity of other chemicals, for example, inhibitors of protein

synthesis. Because the Applicants claims are generic for any drug the Anderson (1991) does not teach away from the invention.

Secondly, when a chemical's biological activity is unknown, scanning for changes in all known markers helps to identify this activity. Thus none of known protein markers should be excluded from the assay.

Thirdly, use of any protein marker(s) disclosed in the prior art in a method of assessing toxicity or efficacy of any identified effect of an identified chemical compound may be patentable if novel and nonobvious. However, none of the claims is limited to a definite drug, or family of drugs, and a marker or a set of markers. The claims are generic and therefore rejected under 35 USC section 103 as written above.

Anderson et al. 1991, see Figure 10 and its description, clearly suggest that the proteome markers can be used to "show quantitative effects of various treatments [any treatment]" on mammalian tissue. In addition, markers of efficacy of claims 85 and 86 of the instant application are listed by Anderson et al. as "protein useful in drug [any drug!] effect studies"; see Table 1 of Anderson et al. 1995, copy enclosed with the previous office Action.

4. Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.
Art Unit 1652
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